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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,972	07/02/2004	Melissa Egbertson	21021YP	1833

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,972	EGBERTSON ET AL.	
	Examiner	Art Unit	
	Susannah Chung	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12 and 18-20* is/are rejected.

7)☒ Claim(s) *13-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/05, 12/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending in the instant application. Claims 21-23 are canceled by preliminary amendment filed 07/02/2004.

Priority

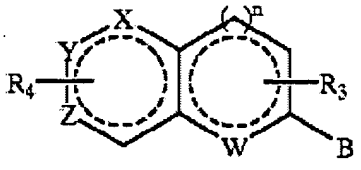
This application is a 371 of PCT/US03/00813, filed 01/13/2003, which claims benefit of 60/349,775, filed 01/17/2002.

Information Disclosure Statement

The information disclosure statements (IDS), filed on 2/22/05 and 12/6/05 have been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Response to Election/Restrictions

Applicant's election *with traverse* of a group of the compound of Formula (I), wherein L is C1-6alkyl and the compounds are used to treat HIV/AIDS is acknowledged.

Applicants arguments have been considered, but are not found persuasive. The traversal is on the ground that the claims do not lack unity of invention because US Pat. No. 5,945,431 preferably teaches 1,6-naphthyridine, while the instant application preferably teaches 1,2-dihydro-1,5-naphthyridine. Although, the prior art does not preferably teach 1,5-naphthyridine, it does disclose it. The prior art teaches a compound of formula (I), 

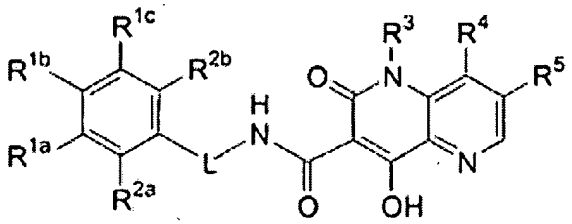
, wherein X and W are nitrogen; R3 and R4 are hydroxyl; and B is CO-N-R, wherein R is alkyl or aryl or heteroaryl, resulting in the core structure of the instant application breaking unity of invention. In addition, a serious burden is placed on Examiner when there is a variable present in the middle of the core

structure. In the instant case, the variable L can result in a multitude of different compounds, thus requiring restriction once unity of invention was broken. Therefore, for the above reasons, the requirement is still deemed proper and is therefore made FINAL.

Scope of the Elected Invention

Claims 1-20 are pending in this application.

The scope of the elected subject matter that will be examined and searched is as follows:

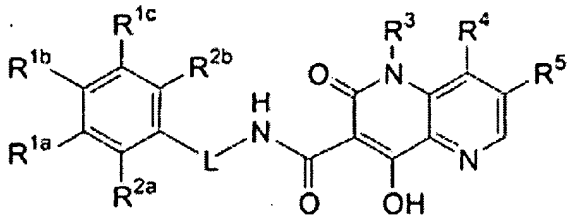
Compounds of formula (I),  ,

depicted in claim 1, page 4, wherein:

L is
(i) a single bond,
(ii) -(C_{1-6} alkyl)-, which is optionally substituted with -C(=O)N(R^aR^b),
(iii) -(C_{0-3} alkyl)-C=C-(C_{1-3} alkyl)-,
(iv) -(C_{0-3} alkyl)—C≡C—(C_{1-3} alkyl)-, or

Scope of Withdrawn Subject Matter

The scope of the withdrawn subject matter that will not be examined and searched is as follows:

Compounds of formula (I),  ,

depicted in claim 1, page 4, wherein:

L is (v) -(C_{0-6} alkyl)-(C_{3-6} cycloalkyl)-(C_{0-6} alkyl)-;

Claim Rejections - 35 USC § 103

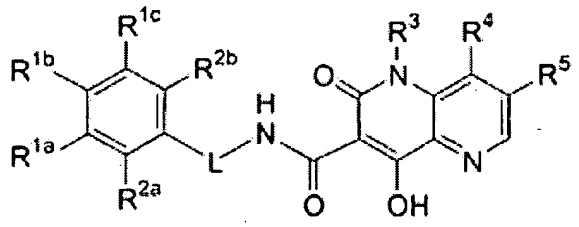
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

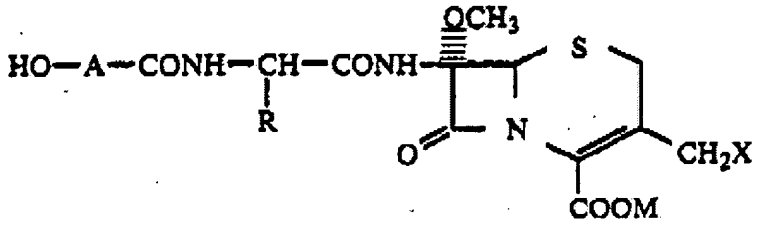
Claims 1-13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al., U.S. Pat. Nos. 4,125,611 (`611 Patent) and 4,226,863 (`863 Patent).

Applicants instant elected invention teaches pharmaceutically active compounds of formula,  , depicted in claim 1, wherein:

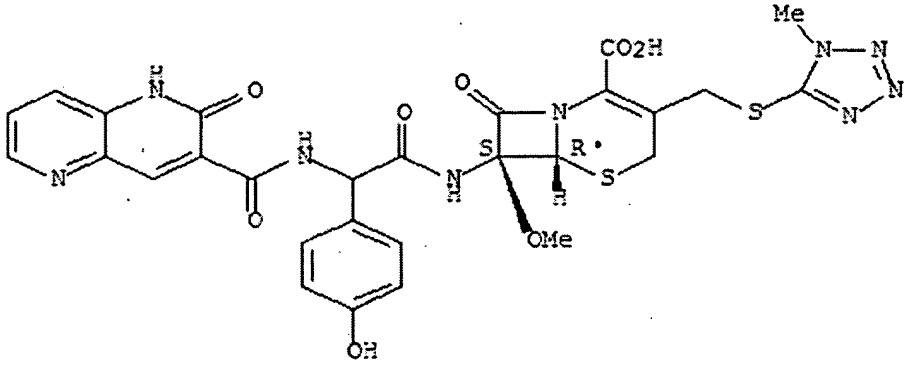
(i) a single bond,
(ii) -(C_{1-6} alkyl)-, which is optionally substituted with -C(=O)N(R^aR^b),
(iii) -(C_{0-3} alkyl)-C=C-(C_{1-3} alkyl)-,
L is (iv) -(C_{0-3} alkyl)—C≡C— (C_{1-3} alkyl)-, or (See Claim 1, pages 4-10).

Determination of the scope and content of the prior art (MPEP § 2141.01)

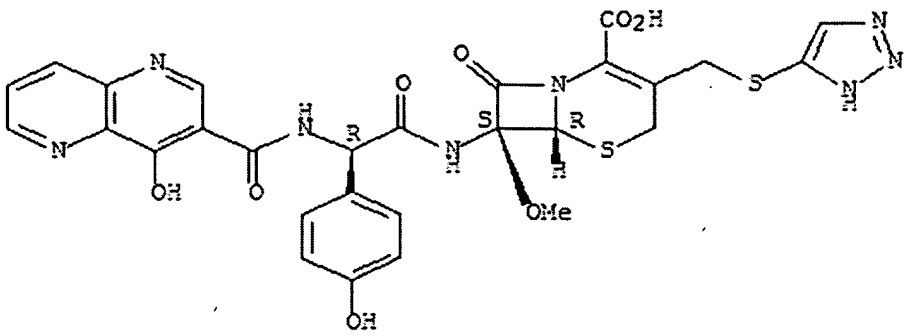
Yamada teaches pharmaceutically active 1,5-naphthyridine compounds of



formula (I), . (See '611 Patent, Claim 1, starting Column 34.) In particular, Yamada teaches the following compounds and their stereoisomers,



, 7-[[[[(1,2-dihydro-2-oxo-1,5-naphthyridin-3-yl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, See CAS RN 64152-45-0 and CAS RN



65759-85-5 and

7-[[[[(4-hydroxy-1,5-naphthyridin-3-yl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-7-methoxy-8-oxo-3-[(1H-1,2,3-triazol-4-ylthio)methyl]- 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, CAS RN 69784-48-1.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Yamada and the instant claims is that the instantly claimed compound is 2-oxo-4-hydroxyl-1,5-naphthyridine, while the prior art teaches 2-oxo-1,5-naphthyridine and 4-hydroxyl-1,5-naphthyridine compounds.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Yamada to make products useful as pharmaceutical agents, wherein both Yamada compounds are combined to form the instantly claimed compound. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art." MPEP 2144.06

Guided by the teaching of Yamada one skilled in the art would be able to make similar compounds by combining both Yamada compounds, i.e. 2-oxo-1,5-naphthyridine and 4-hydroxyl-1,5-naphthyridine, to form the instantly claimed compound, i.e. 2-oxo-4-hydroxyl-1,5-naphthyridine. The motivation would be to prepare similar compounds that are pharmacologically active in the treatment of diseases.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;

3. the state of the prior art;

4. the relative skill of those in the art;

5. the predictability or unpredictability of the art;

6. the amount of direction or guidance presented [by the inventor];

7. the presence or absence of working examples; and

8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 19 and 20 of the present invention below:

(1) The Nature of the Invention

Claims 19 and 20 are directed to:

19. (currently amended) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to either claim 1 ~~or claim 13~~, or a pharmaceutically acceptable salt thereof.

20. (currently amended) A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to either claim 1 ~~or claim 13~~, or a pharmaceutically acceptable salt thereof.

(2) The Breadth of the claims

Claims 19 and 20 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claims 19 and 20 directed to

inhibiting HIV integrase and preventing and treating HIV/AIDS will be interpreted to encompass all types of HIV/AIDS in all patients and all assays.

(3) The state of the prior art

It was known in the art at the time of this application that 1,5-naphthyridines are effective as pharmaceutical agents. In particular, it was known that 1,5-naphthyridines are effective in the treatment of malaria (See McCoustland et al., "1,5-Naphtyiridnes," J. Het. Chem. Vol. 7, No. 3, 1970, where it states that 1,5-napthyridines possess good antimalarial activity against Plasmodium berghei.)

The state of the art at the time of this application does not indicate that 1,5-naphthyridines (1) are effective inhibitors of HIV integrase, (2) can treat or prevent HIV or prevent, treat, or (3) can delay the onset of AIDS in subject in need thereof.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether inhibition of strand transfer activity in a specific HIV Integrase Assay or inhibition of HIV replication could be

reliably and predictably extrapolated to in vivo activity in patients with HIV/AIDS. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that 1,5-naphthyridines exhibit inhibition of strand transfer activity in an HIV Integrase Assay. (See Specification, page 114, Example 29 "HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase.") Also, the specification discloses that 1,5-naphthyridines, in particular Examples 1-27, have IC_{95}'s less than 5 micromolar in an assay for inhibition of HIV replication.

(7) The presence or absence of working examples

As noted in the previous section, the specification discloses the general role of 1,5-naphthyridines in HIV Integrase Assays and inhibition of HIV replication. However, the specification has no working examples, such as in vivo or in vitro studies of the role the instantly claimed compounds play in the prevention or treatment of HIV/AIDS.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role the instantly claimed compounds of formula (I) play in the treatment or prevention of HIV/AIDS, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients would benefit from treatment using which of the many claimed compounds within the scope of the invention with a reasonable expectation of success in treating or preventing HIV/AIDS.

Objections

Claims14-17 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susannah Chung
Patent Examiner, AU 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Date: 27 December 2006